II. REMARKS

Claims 1-42 are pending. Claims 20-31 and 33-42 have been withdrawn pursuant to a restriction requirement. Claims 1-19 and 32 stand variously rejected under 35 U.S.C. 112, second paragraph; 102; and 103.

The specification has been amended herein to correct a typographical error and to delete a hyperlink reference. Further, claim 1 has been amended herein to specify that the mutation is a deletion of more than 60 amino acids from the N-terminal catalytic domain of NS3 and claim 2 has been amended to specify that this deletion includes at least about 200 amino acids of the N-terminal of NS3. (See, *e.g.,* page 11, line 20 and page 27, lines 29-30). In addition, the claims now specify that the polypeptides include a C-terminal portion of NS3. In view of the amendments to claims 1 and 2, claim 3 has been canceled. Claim 13 has been amended as suggested by the Examiner. The amendments are made solely to expedite prosecution, are not intended in any way as an acknowledgment as to the correctness of the Examiner's position.

In view of the foregoing amendments and following remarks, reconsideration of the claims is respectfully requested.

1449 Forms

Although it was indicated on the PTO-326 that initialed and signed copies of the 1449 forms submitted with the IDS on March 5, 2001 were attached to the Office Action, Applicants did not receive these papers. Accordingly, the Examiner is requested to kindly re-send the initialed and signed 1449 forms.

Restriction Requirement

The Restriction Requirement has been deemed proper and made FINAL. Applicants traverse for the reasons of record. (See, Response filed 11/2001).

Specification

The specification was objected to for containing an embedded hyperlink. (Office Action, page 3). By amendment herein the hyperlink has been deleted. In addition, a typographical error on page 2 of the specification has been corrected. In view of the foregoing amendments, the objections have been obviated.

35 U.S.C. § 112, Second Paragraph

Claims 13-15 stand rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite. In particular, it is alleged that the term "fragment" is not clear. (Office Action, page 3).

Applicants thank the Examiner for the suggested amendments and have incorporated them herein. Support can be found, for example, on page 12, line 26 to page 13, line 9. In view of the foregoing amendments and remarks, Applicants submit that the rejections have been obviated or otherwise overcome and, accordingly, request that the rejections under Section 112, second paragraph be withdrawn.

35 U.S.C. § 102

Claims 1-3 stand rejected under 35 U.S.C. § 102 as allegedly anticipated by Bartenschlager. It is alleged that this reference discloses isolated mutant HCV NS3 polypeptides having substitutions and deletions rendering the protease non-functional. (Office Action, page 4).

Applicants traverse the rejection and supporting remarks.

In order to be an anticipatory reference, the single reference cited by the Office must disclose each and every element of the claims. *See, e.g., Hybritech v. Monoclonal Antibodies,* 231 USPQ 81 (Fed. Cir. 1986). Moreover, the single source must disclose all of the claimed elements arranged as in the claims. *See, e.g., Richardson v. Suzuki Motor Co.,* 9 USPQ2d 1913 (Fed. Cir. 1989).

The pending claims are directed to mutant NS HCV polypeptides in which at least 60 amino acids of the N-terminal portion of NS3 have been deleted and which contains an intact C-terminal portion. In contrast, nowhere does Bartenschlager describe such a polypeptide. The N-terminal deletions are, at most, 60 amino acids of NS3. (See, pBSK3525-6062 in Figure 5 and accompanying text). Furthermore, the internal deletions shown in Figure 6 of this reference have fewer than 60 amino acid deleted in the catalytic region and, moreover, necessarily include deletions in C-terminal portions. (See, Figure 6). Accordingly, the pending claims are not anticipated by Bartenschlager and withdrawal of this rejection is respectfully requested.

35 U.S.C. § 103

Claims 1-19 and 32 stand rejected under 35 U.S.C. section 103(a) as allegedly obvious over Bartenschlager in view of EP 0693687 (hereinafter "Houghton") and U.S. Patent No. 5,372,928 (hereinafter "Miyamura"). Briefly stated, the Office Action maintains that the primary reference, Bartenschlager, teaches essentially all the elements of claims 1-19 except different combinations of mutant NS3, NS4a, NS4b, NS5a, NS5b, C (core), E (envelope) and SEQ ID NO:9 and all the elements of claim 32 except the combination of mutant NS3 with a pharmaceutically acceptable excipient. (Office Action page 5). The missing elements are alleged to be disclosed by Houghton and Miyamura. (Office Action, page 6).

Applicants traverse this rejection and address the Examiner's allegations in turn.

The Examiner bears the burden of establishing a *prima facie* case of obviousness. *See, e.g., In re Ryckaert,* 28 USPQ2d 1955, 1956 (Fed. Cir. 1993); and *In re Oetiker,* 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). It is well settled that even when references relied upon teach that all aspects of the claimed invention are known individually in the art, *prima facie* obviousness is not established without some objective reasoning to combine the teachings of the references. *Ex parte Levengood,* 28 USPQ2d 1300 (BPAI 1993).

Even if individual elements of the invention are taught in the prior art, such is not, in and of itself, sufficient to make out a case of *prima facie* obviousness. See, *Symbol Technologies, Inc. v. Opticon, Inc.*, 19 USPQ2d 1241 (Fed. Cir. 1991) ("We do not pick and chose among the individual elements of assorted prior art references to recreate the claimed invention, but rather, we look for some teaching or suggestion in the references to support their use in the particular claimed combination."). As stated by the Court of Appeals for the Federal Circuit, "[i]t is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious." *In re Fritch*, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992). See, also, *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988): "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." Moreover, it is also well established that the Examiner may not combine references to create an obviousness rejection unless there is some suggestion or motivation in the prior art to make the combination. *See, e.g., Arkie Lures, Inc. v. Gene Larew Tackle, Inc.*, 43 USPQ2d 1294 (Fed. Cir. 1997); *In re Oetiker, supra.*

Applicants submit that the combination of references does not teach or suggest all the elements of the pending claims. Moreover, the cited combination is based on impermissible hindsight reconstruction and, in addition, that there is no suggestion or motivation in the cited references to combine them as suggested by the Office. Thus, a *prima facie* case of obviousness has not been presented by the Office.

The requisite motivation to reasonably lead one of skill in the art to the claimed methods is utterly lacking from all of the cited references. With regard to Bartenschlager, Applicants reiterate that this reference does not teach a polypeptide in which more than 60 amino acids of the N-terminal portion of NS3 have been deleted and which contains the C-terminal portion. Nor does this reference teach or suggest mutants in which the catalytic domain is disrupted due to the deletions. Indeed, with regard to the internal deletions, Bartenschlager states "we cannot decide whether the [internal] deletions

affected the proteinase activity or accessibility of the cleavage site..." (See, page 3840, second column). Thus, Bartenschlager fails to disclose the polypeptides as recited in the pending claims.

The secondary references do not cure the deficiencies of Bartenschlager. Indeed, neither Houghton and Miyamura disclose the claimed NS3 mutant polypeptides. Houghton is directed to combination HCV antigens comprising antigen from the core domain of HCV and an additional HCV antigen, for example C33c, an antigen extending from approximately amino acids 1192 to 1457 of NS3. Thus, unlike the claimed mutant polypeptides, C33c lacks C-terminal amino acids of NS3 (which itself extends from approximately 1050 to 1640 of an HCV polypeptide). For its part, Miyamura is silent as to any deletions in NS3. Thus, there is no description or demonstration in any of the references regarding an NS3 mutant polypeptide lacking more than 60 N-terminal amino acids, as is claimed by Applicants.

Further, the alleged suggestion in Bartenschlager that the serine proteinase of HCV may represent a novel target for antiviral drug development cannot be used as a basis for finding motivation to combine Bartenschlager with Houghton and/or Miyamura or as a basis for finding a reasonable expectation of success. (Office Action, page 6, citing page 3843, second column, last paragraph of Bartenschlager). In this speculative statement, Bartenschlager is referring to development of drugs that target this region of HCV, not to the preparation of immunogenic or pharmaceutical compounds comprising HCV polypeptides as described in Houghton and Miyamura. Thus, the Office has not pointed to anything in the references that would lead one of skill in the art to combine them as suggested or that such a combination would reasonably lead one of skill in the art to the claimed subject matter. Accordingly, the 103 rejection appears to be based on either an "obvious to try" standard or on hindsight reconstruction made with the benefit of Applicants' disclosure, which does describes and demonstrates the making of the claimed NS3 mutant polypeptides and compositions comprising these polypeptides. Neither

hindsight reconstruction nor "obvious to try" are legitimate tests of patentability. See, *In re Fine*, 5 USPQ2d at 1599 and *In re Dow Chem.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988).

In sum, the Office has not established a *prima facie* case of obviousness and withdrawal of these rejections is respectfully requested.

III. CONCLUSION

In view of the foregoing amendments, Applicants submit that the claims are now in condition for allowance and request early notification to that effect.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 18-1648.

Please direct all further communications regarding this application to:

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Respectfully submitted,

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Version Showing Changes Made to the Specification

The paragraph beginning on line 1 of page 2 has been changed as follows:

--Virus-specific T lymphocytes, along with neutralizing antibodies, are the mainstay of the antiviral immune defense in established viral infections. Whereas $CD8^+$ cytotoxic T cells eliminate virus-infected-cells, $CD4^+$ T helper cells are essential for the efficient regulation of the antiviral immune response. $CD4^+$ T helper cells recognize specific antigens as peptides bound to autologous HLA class II molecules (viral antigens or particles are taken up by professional antigen-presenting cells, processed to peptides, bound to HLA class II molecules in the lysosomal compartment, and transported back to the cell surface). Several observations support an important role of $CD4^+$ T cells in the elimination of HCV infection. Tsai *et al.*, 1997 Hepatology 25:449-458; Diepolder et al 1995 Lancet 346: ~~1--6-1009~~ 1006-1007; Missale et al 1996 JCI 98: 706-714; Botarelli et al 1993; Gastro 104: 580-587; Diepolder et al 1997 J.Virol 71: 6011. Immunogenic peptides usually have a minimal length of 8-11 amino acids. However, since the peptide binding groove of HLA class II molecules seems to be open at both ends, longer peptides are tolerated. Thus peptides eluted from HLA class II molecules are typically in the range of 15-25 amino acids. HLA class II molecules are extremely polymorphic and each allele seems to have its individual requirements for peptide binding. Thus the HLA class II repertoire of a given individual determines which viral peptides can be presented to T cells. Recognition of the specific HLA-peptide complex by the T cell receptor accompanied by appropriate costimulatory signals lead to T cell activation, secretion of cytokines, and T cell proliferation.--

The paragraph beginning on line 24 of page 19 has been replaced with the following:

--Another method of establishing percent identity in the context of the present invention is to use the MPSRCH package of programs copyrighted by the University of Edinburgh, developed by John F. Collins and Shane S. Sturrok, and distributed by IntelliGenetics, Inc. (Mountain View, CA). From this suite of packages, the Smith-Waterman algorithm can be employed where default parameters are used for the scoring table (for example, gap open penalty of 12, gap extension penalty of one, and a gap of six). From the data generated, the "Match" value reflects "sequence identity." Other suitable programs for calculating the percent identity or similarity between sequences are generally known in the art, such as the alignment program BLAST, which can also be used with default parameters. For example, BLASTN and BLASTP can be used with the following default parameters: genetic code = standard; filter = none; strand = both; cutoff = 60; expect = 10; Matrix = BLOSUM62; Descriptions = 50 sequences; sort by = HIGH

SCORE; Databases = non-redundant, GenBank + EMBL + DDBJ + PDB + GenBank CDS translations + Swiss protein + Spupdate + PIR. Details of these programs can be found on the world wide web~~at the following internet address: http://www.ncbi.nlm.gov/cgi-bin/BLAST~~.--

Version Showing Changes Made to Claims

1. (Amended) An isolated mutant non-structural ("NS") HCV polypeptide comprising a polypeptide having a [mutation in] deletion of more than 60 amino acids from the [catalytic domain] N-terminal portion of NS3, wherein said [mutation] deletion functionally disrupts the catalytic domain of NS3 and further wherein said polypeptide comprises the C-terminal portion of NS3.

2. (Amended) The polypeptide of claim 1, wherein the [mutation comprises a] deletion is at least 200 amino acids.

13. (Amended) The polypeptide of claim 12, wherein the second viral polypeptide comprises an HCV Core polypeptide ("C") or immunogenic fragment thereof.